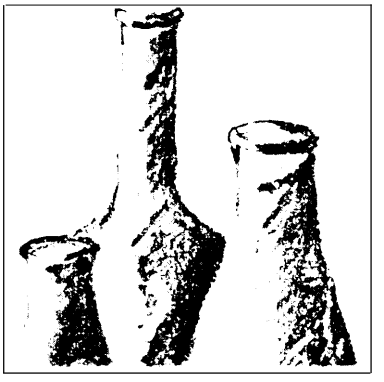
The Costs of Pharmaceutical R&D 3

This chapter brings together existing evidence on the cost of bringing new pharmaceuticals to market. It begins with background on how to measure such costs and then moves to an assessment of existing studies of research and development (R&D) costs. These studies are retrospective: they estimate the costs of R&D for pharmaceutical products developed and brought to market in the past. R&D costs can change quickly as underlying scientific, technical, or regulatory conditions change, so it is dangerous to predict much about the future, or even about today's R&D costs, from studies of past costs. In the last part of the chapter, the Office of Technology Assessment (OTA) examines recent trends in some critical components of the cost of bringing new drugs to market.

A FRAMEWORK FOR ESTIMATING R&D COSTS

R&D is an investment in a potential future stream of revenues from the sale of successful new drugs. Unlike other kinds of investments, such as a new manufacturing plant, the success of a pharmaceutical R&D investment is highly uncertain and may take many years to be realized. The investors in pharmaceutical R&D must be able to "expect" not only to recoup their actual cash outlays for R&D but also to be compensated for the risk they took of losing their investment altogether and for the time they spent waiting for the investment to pay off. Without such an expectation, no investor would put his or her money on the line.



The full cost of the R&D investment can be thought of as the minimal 'expected' payoff required to induce the investor to lay out the money at each step of the research project. The ' 'expected' payoff does not mean an assured payoff; rather, it means the minimal payoff required from the drugs that successfully reach the market after taking into account the chances of success and failure and the expected development time involved.

The full cost of bringing a new drug to market, as defined above, is clearly higher than the cash outlays spent to discover and develop successful new drugs. It also includes the cash outlays spent on projects that fail.[1] And, it must include the *opportunity cost of capital, the* rate of interest that dollars invested at a given level of risk must earn in exchange for being tied up in the investment (59,285).

The opportunity cost of capital for pharmaceutical R&D is higher than the interest rate on safe investments, such as insured bank deposits or government bonds, but just how high the cost of capital for pharmaceutical R&D projects is depends on how investors evaluate the risks of these investments, (See appendix C for a detailed discussion of the cost of capital.) The risk and, therefore, the cost of capital varies across different projects and even within the same R&D project at different stages of development. The cost of capital for any investment also varies from year to year with underlying changes in the risk-free rate of interest (e.g., on bank deposits). Thus, the full cost of R&D varies widely over time and across projects.

To measure the full cost of bringing a new drug to market, all outlays required to achieve the successes (including spending on projects that fail) must be compounded (or capitalized) at an interest rate equal to the cost of capital, to their present value (or capitalized value) at the date of market approval. For example, $1 million invested 1 year ago should be worth $1.1 million today if the cost of capital for that investment was 10 percent per year.

Note again that the full cost of bringing a new drug to market is much higher than the amount of money companies must actually raise to fund R&D projects. To pursue R&D, companies must raise only enough cash to cover the actual outlays associated with the successful and unsuccessful projects. Estimating the full cost of bringing a new drug to market, by contrast, provides a way of gauging ho w much money must be earned from the successful drugs, once they reach the market, to justify the research outlays.

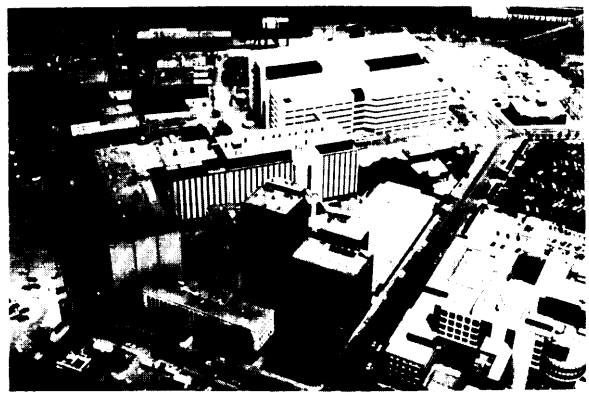


Photo credit: THE UPJOHN COMPANY

R&D expenditures include substantial investment in research facilities and equipment. The Upjohn Company recently built this new addition to its research facilities, the '(white" building located at the top of the photograph. It encompasses more than 700,000 square feet, was constructed at a cost of $120,000 million, and will house more than 500 scientists.

EXISTING STUDIES OF R&D COSTS

Two major approaches have been used to estimate the cost of bringing new drugs to market. One approach examines project-level data acquired from pharmaceutical firms. The second approach analyzes R&D expenditures and new products at the industry level. Table 3-1 contains a summary of selected pharmaceutical R&D cost studies of both kinds—project-level and industry-level—listed in the order of the R&D period studied.

Project-level studies try to measure costs incurred at each stage of development and the percent of drugs that will successfully pass each stage, and then use these calculations to arrive at a final cost estimate. The key advantage of the project-level approach is that, if sufficiently

[1] when the full cost of R&D is estimated with historical data, averaging of outlays across winners and losers must take place across the entire industry, or at least a good part of it, because individual companies may have unusual experiences. For example, a company could have mismanaged its research, leading to relatively few successes and high outlays per success. Though investors in that company might have lost money, they need not be rewarded for their bad judgment. The experience of the industry as a whole is a good basis for estimating the true (and uncontrollable) probability of success and failure of R&D projects.

Table 3-I—Summary of Selected Pharmaceutical R&D Cost Studies

Study	Sample years	Estimation method	Data source	Estimated R&D costs	Constant dollar year	Opportunist y cost of capital	Preclinical costs	Treatment of unsuccessful projects
Project-level studies								
Schnee, 1972	1950-67 (market introductions)	Average development cost and time for 75 rejects marketed in one Plarge firm.	R&D project cost data reported by one firm.	NCEs:$534,000.	Current dollars	0%	Not included	Not included
Hansen, 1979	1963-75 (projects entering human testing)	‹&D expenditure profile ›uilt for sample of ap-›roximately 67 self-origi-ıated NCEs, not all ;uccessful.	NCE sample and R&D project expenditures from 14-firm survey.	$54 million	1976	8%	Assumed to be 530/' (allocated over 3 years nor to IND filing).	Estimated 12.5% NCE success rate.
DiMasi et al.,1991	1970-82 (projects entering human testing)	R&D expenditure profile built for sample of 93 self-originated NCEs, not all successful.	NCE sample and R&D project expenditures from 12-firm survey.	$231 million	1987	*9%*	Estimates from reported preclinical and clinical period expenditures.	Estimated success rate by phase for sample NC ES.
Industry-level studies								
Baily, 1972	1949-69 (market introductions)	Regression of total U.S. drug introductions in U.S. firms 1949-69 on total research expenditures (lagged 5 years), FDA regulation stringency, and a measure of depletion of research opportunities.	Total R&D data: PMA survey. New drug introductions: Paul de Haen, Inc.	Pre-1962: $2.5 million. Post-1962: $6 million.	1958	0%	Implicit	Implicit
Sctwartzman, 1976	1966-72 (NCE approvals)	Allocation of total R&D expenditures (lagged 5 years) to NCEs introduced in 1966-72.	R&D expenditures: PMA survey.	$24.4 million	1973	0%	Assumed to be 50%	Implicit
Wiggins, 1987	1970-85 (NCE approvals)	Regression of NCE introductions on total R&D expenditures (lagged 4 years); FDA approval times, by therapeutic class. Adjuste d for Hansen's time profile.	NCEs: FDA. R&D expenditures: PMA surveys.	$108 million[a]	1986	8%	Implicit	Implicit
Grabowski & Vernon, 1989	1970-79 (NCE approvals)	Analysis of industry R&D expenditures and NCE production. R&D time profiles modified from regression estimates.	NCEs: FDA. Total R&D expenditures: PMA surveys.	$125 million	1986	9%	Implicit	Implicit

[a] Wiggins originally reported $125 million; adjustment for technical error changes the number to $108 million (DiMasi et al; 1991).

KEY: NCE = new chemical entity; IND = investigational new drug; FDA = U.S. Food and Drug Administration; PMA = Pharmaceutical Manufacturers Association.

SOURCES: J.E. Schnee, "Development Cost: Determinants and Overruns," *Journal of Business* 45(3):347-374, 1972. M.N. Baily, "Research and Development Costs and Returns: The U.S. Pharmaceutical Industry," *Journal of Political Economy 80(I)* :70-85, *1972.* D. Schwartzman, *The Expected Return From Pharmaceutical Research* (Washington, DC: American Enterprise Institute, 1975). R. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes," Issues *in Pharmaceutical Economics,* R.A. Chien (cd.) (Lexington, MA: D.C. Heath and Co., 1979). S.N. Wiggins, *The Cost of Developing* a New *Drug* (Washington, DC: Pharmaceutical Manufacturers Association, 1987). H.G. Grabowski and J.M. Vernon, "A New Look at the Returns and Risks to Pharmaceutical R& D," *Management Science 38(7):804-821,* July 1990. J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

reliable data can be obtained, it provides the most detailed view of the costs of particular projects and overall development costs. These studies look at a sample of new product introductions (virtually always new chemical entities (NCEs)[2]) and use project cost data obtained from companies to estimate the average cost of bringing a product to market. Although Clymer (79) and Schnee (367) took this project-level approach in early studies, they calculated only the cash R&D outlays of a single firm, and Schnee did not consider the cost of failures. These studies are therefore not considered further.

The prototype of project-level R&D cost estimation is a pair of studies published by Hansen in 1979 and DiMasi and colleagues in 1991 (109,175). They used very similar methods and data sources to estimate the present value in the year of U.S. market approval of the costs of discovering and developing NCEs. The results of these studies have been used to estimate net returns to R&D and to estimate recent changes in the cost of developing new drugs.

Industry-level studies examine the relationship between new product introductions and industry research expenditures. An estimated regression equation that predicts NCE introductions as a function of R&D expenditures in previous years as well as other external factors (such as regulatory controls) is then solved for the R&D expenditures required to bring one additional NCE to market.[3]

The advantage of these industry-level studies is that data on product introductions and research expenditures are verifiable and readily available at the industry level. The disadvantage is that the introduction of NCEs in any year must be related to a pattern of past R&D expenditures that is complex and often beyond estimation with the limited number of years of data available. This approach was pioneered by Baily (32), but the cost estimate from that study is based on very old data that are not converted to present values.

A recent estimate based on a study by Wiggins (520) is the most comprehensive analysis using this approach. Wiggins followed the general method first used by Baily, but Wiggins had more data at hand and used less restrictive assumptions about the nature of the relationship between expenditures and new drug production. Therefore, this chapter focuses on the Wiggins study.

Grabowski and Vernon (159) also used published aggregate R&D expenditure data to estimate the cost of successful drug development. Though Grabowski and Vernon did not estimate development time profiles with statistical analysis, their estimate provides another point of reference for comparison among methods, and it is also summarized here.

The Hansen and DiMasi Studies

METHODS

The two studies by Hansen (175) and DiMasi (109) are based on samples of NCEs frost entering human testing in specified time periods. The sample of NCEs for each study was selected from a set of data on NCEs constructed and maintained by the Tufts University Center for the Study of Drug Development (CSDD) from an ongoing triennial survey of over 40 pharmaceutical fins. The early study examined approximately 67 NCEs, discovered and developed by 14 U.S. pharmaceutical firms that first entered human trials between 1963 and 1975. The second study

2 DiMasi defines ''NCE'' as ''a new molecular compound not previously tested in humans" (107). In keeping with DiMasi's definition this report uses the term NCE to refer to both therapeutic drugs and biological.

3 Industry-level analyses are therefore estimates of marginal costs of NCE production. As DiMasi observed, marginal costs and average costs are not likely to be equal unless R&D is subject to constant returns to scale (109). In an R&D-intensive pharmaceutical firm, there may be substantial economies of scale. particularly at low levels of expenditure. However, from the standpoint of the industry as a whole, marginal costs may more closely approximate average costs. A more important criticism of the marginal cost measure is that the marginal NCE (i.e., the next one that would be brought forth by an infusion of new R&D expenditures) is not determined by costs alone but by the present value of net returns. The marginal NCE might be a low-cost project with low revenue prospects. Therefore, marginal research cost does not have much meaning from the standpoint of R&D decisions.

examined 93 NCEs, discovered and developed by 12 U.S. fins, that were first tested in humans between 1970 and 1982 (109).

Both studies looked only at NCEs that were actually discovered by the firms themselves (i.e., self-originated), not licensed from other companies, and the samples in both studies included unsuccessful as well as successful NCEs. Products acquired through joint ventures or licenses were excluded because part of the costs of these R&D projects would have been borne by other firms and could not be measured easily.

The study authors surveyed the firms sponsoring the sampled NCEs for information about the costs incurred from year to year as each NCE traveled through the drug development process. Many of the sampled products were abandoned during the clinical testing phase, and the costs were adjusted for these abandonments. With year-by-year estimates of spending for each project, the authors could build a time profile of expenditures throughout the development period. These time profiles were then combined with information about the survival experience of the NCEs under study to estimate the average cash outlays[4] for clinical research.

A portion of R&D cost is devoted to the discovery of NCEs. These basic and preclinical research activities cannot be allocated to specific NCEs, so the authors of each study asked firms to report information that would allow estimation of preclinical research expenditures. In the early study, firms were asked to report total NCE R&D expenditures in the United States between 1962 and 1975 as well as "basic research" expenditures.[5] Overall, firms reported that 51 percent of all NCE R&D expenditures were for basic research, so Hansen assumed an amount equal to the total average development period cost went to basic research in the preclinical period, spread equally over 3 years prior to the initiation of clinical testing.

DiMasi used a more involved methodology to estimate both the amount of preclinical cost and the timing of those costs. Firms reported total self-originated NCE R&D expenditures and preclinical research expenditures between 1970 and 1986. Preclinical expenses averaged 66 percent of total self-originated NCE research. This estimate was revised to 58 percent to account for trends in the data over the time period on which the estimate was based.[6] These estimated preclinical costs were spread evenly over 42.6 months prior to the initiation of the clinical period.[7]

The estimated cash outflows, spread over the discovery and development periods according to the time profile reported by companies, were converted to their present value in the year of market approval. The early study used a real (inflation-adjusted) cost of capital of 8 percent; the later study used 9 percent.

RESULTS

Table 3-2 shows how the actual estimated cash expenditures (in 1990 constant dollars) changed between the two studies. Total cash outlays per successful new NCE were estimated at $65.5 million (1990 dollars) by Hansen and at $127.2 million by DiMasi, a 94 percent increase in estimated real (inflation-adjusted) outlays per successful new drug over the period of the two studies. If the midpoint of the study years is used to calculate the rate of increase in cash outlays,

[4] The reported expenditures don't correspond exactly to cash outlays because charges for indirect costs, overhead, or capital equipment and facilities may be made using allocation or depreciation methods that don't correspond in time to actual cash outlays. The term "cash costs" is used here to differentiate the reported expenditures from their present values in the year of market approval.

[5] Development costs included clinical costs and short-term preclinical animal studies.

[6] Since clinical period expenditures occur later than preclinical expenditures, the ratio of preclinical period real R&D to total real R&D expenditures overestimates the true preclinical period contribution when total expenditures are rising (109).

[7] The length of the preclincial period was estimated from data in the CSDD database on NCEs approved for marketing by the U.S. Food and Drug Administration (FDA) in the years of the study. The preclinical period is defined in that database as the length of time from synthesis of a drug to the beginning of human clinical studies.

Table 3-2-Cash Outlays per Successful New Chemical Entity: Hansen and DiMasi ($ 1990 millions)[a]

Study	Study years (midpoint)	Clinical cost	Preclinical/discovery cost	Preclinical/discovery As percent of total cost	Total cash outlays per success
Hansen, 1979. ...., . .	1963-75 (1969)	$29.9	$35.6	54%	$65.5
DiMasi et al., 1991	1970-82 (1976)	53.8	73.4	58	127.2
Rate of increase (%). . .		79	106		94

a All estimates were adjusted for inflation using the GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, adapted from R. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes," *Issues in Pharmaceutical Economics,* R.A. Chien (cd.) (Lexington, MA: D.C. Heath and Co., 1979); J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, 1991.

this pair of studies suggests that real R&D cash outlays per successful NCE increased at an annual rate of about 9.5 percent in the study years.[8]

The increase in cash outlays per success is moderated by an improvement in the success rate of the drugs in the two study cohorts. Whereas Hansen projected an ultimate success rate from human testing to approval by the U.S. Food and Drug Administration (FDA) of 12.5 percent, DiMasi and colleagues estimated about 23 percent of the projects would be successful. Without this improvement, the increase in cash outlays per success would be even higher.

Because the estimated ratio of preclinical costs to clinical costs was higher in the later study than in the early study, the increase in real cash outlays is somewhat greater for preclinical costs than for clinical period costs, but the annual rates of increase were not very different-10.3 percent per year for preclinical costs compared with 8.3 percent per year for clinical period costs.

Total R&D costs capitalized to the date of approval for marketing increased from $108 million to $259 million (in 1990 dollars) over the course of the two study periods, an inflation-adjusted increase of 139 percent, or 12.4 percent per year from the midpoint of the early study (1969) to the midpoint of the later study (1976). The even more rapid increase in fully capitalized costs was due to cost-increasing changes in two components of the estimates:

- An increase in the estimated cost of capital from 8 percent in the early study to 9 percent in the later study.
- An increase in the total development time from 9.6 to 11.8 years, led by a longer preclinical period in the later study (42.6 months, compared with 36 months) and a longer period of regulatory review once a new drug application (NDA) is filed with the FDA (30.3 months compared with 24 months).

The change in the assumed cost of capital alone would account for little of the increase in total capitalized costs. OTA reconstructed Hansen's cost analysis using a 9 percent cost of capital. This change, in the absence of any others, increascd Hansen's total cost estimate by only 5 percent to

[8]Comparison of the midpoints of the study years may understate the true difference in time between the studies and may therefore overstate the rate of change over the time period. Although the database from which the sample of NCES in each study was drawn shows the median years for self-originated NCES receiving investigational new drugs in the two studies were 7 years apart (107), the cost estimates in the early study were based more heavily on the older NCES in the sample than were the cost estimates in the second study (176). If a steady upward trend in the real cost of R&D was occurring throughout the decades of the two studies, the cost estimates of the early study would be biased downward.

approximately $114.8 million (in 1990 dollars). Increasing the discovery/development period to match that of the DiMasi study without any other changes would increase Hansen's total cost estimate to $122.7 million (13 percent higher than the baseline estimate). Together, a higher cost of capital and a longer R&D time profile (in the absence of any other changes) increased Hansens estimated cost to $132.9 million (in 1990 dollars), only 23 percent higher than the baseline estimate. Thus, without the very large changes in estimated cash outlays over the two periods, the inflation-adjusted rise between the two periods in R&D costs per success would have been relatively modest.

The Wiggins Study

Wiggins regressed the total number of NCEs that the FDA approved between 1970 and 1985 on the estimated total NCE-oriented research spending in previous years[9] and on the average delay in NDA approval times for drugs approved 5 years earlier. The regression equation was then transformed into an estimate of the extra cash research outlay required to bring forth one additional NCE. This estimate of marginal R&D cash outlay per additional NCE was $75 million in 1990 dollars.

Wiggins' analysis is based on NCE approvals for marketing, not NCEs entering human testing. If the average time from the filing of an investigational new drug (IND) application to approval of the drug by the FDA was 6.5 years (as Hansen's early survey indicated), then Wiggins' sample corresponds to NCEs first entering clinical testing between roughly 1963 and 1979, a period that overlaps substantially with the Hansen study (1963 to 1975). Thus, Wiggins' estimate of $75 million in cash costs is roughly in line with Hansen's estimate of $65.5 million, especially when one considers Wiggins' analysis probably covers a somewhat more recent population of NCEs than does Hansen's.

Wiggins' NCE sample is different from Hansen's, however, because it includes licensed-in products as well as self-originated NCEs. It is unknown how the full costs of discovery and development for licensed-in products compare with those of self-originated drugs. Though the cost of developing licensed-in products is likely to be lower for the licensee, if the licenser is a Pharmaceutical Manufacturers Association (PMA)-member company, then Wiggins' method would have captured the early costs.

Although Wiggins converted cash R&D costs to their present value at the time of market approval, he did so by assuming the cash costs followed Hansen's estimated time profile.[10] Like Hansen, Wiggins used an 8 percent cost of capital. Starting with higher out-of-pocket expenses, Wiggins necessarily concluded the full cost of bringing an NCE to market is higher than Hansen predicted. In 1990 dollars, Wiggins' estimated cost of discovery and development of a new NCE is $123.4 million[11] compared with $108 million estimated by Hansen (175).

The Grabowski and Vernon Study

Grabowski and Vernon (160) also used annual aggregate R&D data reported by PMA to estimate the average cost of developing new NCEs approved by the FDA for marketing during the 1970s. Like Wiggins, Grabowski and Vernon estimated the cost per NCE for both self-originated and licensed-in drugs. They assigned

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9 The average research expenditures for NCEs in the third, fourth, and fifth year prior to FDA market approval as reported to the Pharmaceutical Manufacturers Association was used as the measure of research expenditure.

10 Since Wiggins' analysis included licensed-in as well as self-originated drugs, he should have used a different, and probably shorter, time profile for the licensed-in drugs. Data on development times for approved licensed-in drugs suggest they are substantially shorter than the development times for approved self-originated products (107), which suggests lower costs to the licensee. Had Wiggins applied a different profile to the licensed-in drugs, his estimate of total capitalized cost would have been lower.

11 This value disagrees with Wiggins' estimate, $144 million in 1990 dollars. As discussed by Woltman (524) and DiMasi et al. (109), Wiggins made an error in calculating the total capitalized cost. OTA'S re-estimate, $123.4 million, is slightly lower than DiMasi's recalculation, $124.7 million in 1990 dollars, because of differences in price indexes used.

R&D expenditures in each year between 1962 and 1978 to product introductions in the years 1970-79 using assumptions about the application of each year's expenditures to the future years' introductions. For example, Grabowski and Vernon assumed that in 1965, 10 percent of R&D expenditures for NCEs was spent on drugs introduced in 1970, 10 percent on drugs introduced in 1971, etc.[12]

This weighting scheme was then used to estimate the cost of introductions in each year. Compounding these values to the date of market introduction at 9 percent, Grabowski and Vernon estimated the mean cost per successful NCE approved by the FDA between 1970 and 1979 was $142 million in 1990 dollars. Because the weighting scheme assumes a total discovery/development period of 8 to 12 years (lengthening over the period of study), this estimate corresponds to NCEs first entering human testing in the period roughly bounded by 1965 and 1972. This period falls within the bounds of Hansen's study years.

Whereas Hansen's total estimated cost in 1990 dollars with a 9-percent discount rate is $114.8 million for drugs entering testing in the period, Grabowski and Vernon estimated an average cost of $142 million. For NCEs approved in 1975, Grabowski and Vernon estimated cash R&D outlays of $86.7 million in 1990 dollars compared with $65.5 million estimated by Hansen.

Comparison of Estimates

The studies discussed above are best compared by standardizing for constant dollar year and cost of capital, chosen here to be 1990 and 9 percent. Table 3-3 shows the estimates from each reviewed study.

The three studies of research conducted on NCEs frost entering clinical testing in the 1960s and early 1970s use different methods and arrive at estimates differing by up to 25 percent. Since the methods used in each study are not completely independent,[13] more congruence might have been expected.

Table 3-3-Estimates oft he Full Cost of Bringing a New Chemical Entity to Market[a] ($ 1990 millions)

Study	First year of clinical testing (midpoint) 1963-75 (1969)	1970-82 (1976)
Hansen, 1979	$114.8	—
DiMasi et al., 1991	—	$259
Wiggins, 1987	131.5	—
Grabowski and Vernon, 1990	142	—

a All estimates were adjusted for inflation using the GNP implicit price deflator and were calculated at 9 percent cost of capital.

SOURCE: Office of Technology Assessment, 1993.

Because neither Wiggins nor Grabowski and Vernon differentiated between licensed-in and self-originated drugs, their estimates should be lower, or at least no higher, than those of Hansen. Yet the cash outlays estimated in both industry-level studies are higher than those of Hansen. Hansen estimated cash outlays per successful NCE of $65 million; Wiggins estimated $75 million; and Grabowski and Vernon estimated $86.7 million.

VALIDITY OF R&D COST ESTIMATES

All of the R&D cost studies described above begin with estimates of R&D cash outlays in each phase of development, the time required to complete each phase, and the success rate for projects in each phase of the process. These estimated cash flows are then capitalized with a cost of capital that differs among studies. The validity of the studies rests ultimately on the accuracy of the estimates of cash outlays and the timing of those outlays. In this section, OTA analyzes the validity of the estimates of cash

12 These assumptions were based in part on a regression estimate Thomas made in 1986 (421).

13 Hansen used the sample firms' self-reported data on R&D expenditures to estimate basic research costs to their present value; Wiggins used Hansen's time profile generated from a survey of companies' NCE introductions to capitalize costs, and Grabowski and Vernon's time profiles were based largely on data supplied by the CSDD NCE database, the same database from which Hansen's sample was drawn and from which estimates of Hansen's R&D time profile were partially drawn.

outlays, their timing, and the success rates from stage to stage in the development process.

Are the estimates of cash outlays accurate? OTA addressed this question in two ways. First, we critically assessed the validity of the methods and data sources used to arrive at the estimates and the potential importance of departures from full validity. Second, we attempted to corroborate the findings with data from independent or semi-independent sources.

The assessment of validity of the methods concentrates on the project-level studies of Hansen (175) and DiMasi (109) for two reasons. First, the DiMasi study offers the most recent estimate which industry representatives and others have quoted widely as the definitive estimate of research costs (325). Second, the other studies based on aggregate R&D expenditures draw from the project-level analyses of Hansen and DiMasi for estimates of the time profile of development and are therefore partially dependent on them.

Validity of Study Methods

The validity of the project-level studies depends on three aspects of the study methods:

- Sample of fins;
- Sample of NCEs; and
- Accuracy of survey responses regarding:
  1. clinical period cash outlays,
  2. preclinical period cash outlays,
  3. phase-specific development times, and
  4. phase-specific success rates.

THE SAMPLE OF FIRMS

Both Hansen and DiMasi examined NCEs originated at U.S .-owned, research-intensive pharmaceutical fins. Hansen's early study included 14 firms willing to respond to the survey; DiMasi's later study included 12. Because the samples were predominantly large well-established companies in both surveys, the reported R&D costs may not reflect the cost experience of small and relatively young firms,[14] although the direction of potential biases between large and small firms is unknown.[15] Even if systematic differences in R&D costs by firm size or total R&D commitment do exist, they should not survive for long, for the industry would gradually reorganize to operate at the most efficient level. The responding firms in the DiMasi study represented 40 percent of domestic R&D, as measured by PMA, and the distribution of R&D by therapeutic class in these firms was virtually identical to the distribution of R&D in the U.S. pharmaceutical industry as a whole.[16] Thus, the sample of firms appears to pose no serious threat to the validity of the study.

THE SAMPLE OF NCES

Both studies selected a sample of NCEs that originated within the company's U.S. research organizations. NCEs were selected from a database maintained by CSDD of new products under development. Probability samples were drawn from the universe of NCEs in the CSDD database, but some nonresponding companies could have biased the sample. Furthermore, neither study reported the within-fro response rate. If firms failed to provide data on some NCEs for which data were poor, or if they selectively reported on NCEs for some other reason, the sample of NCEs could be biased. Again, the effect of such potential biases on cost estimates cannot be judged.

The adequacy of the sample size to reliably predict costs is determined by the underlying variation in the costs to be measured. The sample size in the Hansen study was 65 to 70 NCEs. The precise NCE sample size was not reported. DiMasi examined 93 NCEs. The higher the

14 The emergence of dozens of small biotechnology firms performing pharmaceutical research in the 1980s would make this point more salient for periods later than those studied by Hansen and DiMasi.

15 Pharmaceutical firms may experience decreasing returns to scale of R&D at low levels of R&D (213). Comanor found the marginal productivity of research personnel is inversely related to the size of the firm (85), but after controlling for R&D levels, Jensen did not find such a relationship (213).

16 Hansen did not provide estimates of the proportion of domestic R&D accounted for by the 14 firms in his sample.

Table 3-4-Confidence Intervals for Clinical Period Cash Outlays in DiMasi Study ($ 1987 millions)

Phase	Mean cost[a]	Standard deviation	95% confidence Interval for mean	Probability that true mean is within 10 percent of estimated mean
i	$2,134	$4,519	$1,184- 3,084	0.34
ii.”.”.”.”.”.”.-.”.”.”. : :	3,954	5,230	1,729- 4,179	0.36
Iii.	12,801	13,974	8,236-17,366	0.41
Long-term animal.	2,155	2,411	1,480- 2,830	0.46
Other animal.	648	1,183	49 - 1246	0.17

a Calculated for all new chemical entities entering the phase.

SOURCE: Office of Technology Assessment, 1993, based on data provided in J.A.DiMasi, R.W. Hansen, H.G. Grabowski, et al., “The Cost of Innovation in the Pharmaceutical Industry,” *Journal of Health Economics* 10:107-142, 1991.

underlying variation in costs, the larger the sample size must be to meet any required level of precision. Hansen did not report on the observed variation in costs among NCEs, so there is no way to evaluate the precision of his estimate,

DiMasi did report the sample standard deviation of cash outlays in each phase of the clinical period. Table 3-4 shows the standard deviations, the 95-percent confidence intervals[17] for the true mean cash outlay in each clinical phase, and the estimated probability that the true mean cash outlay in each phase lies within 10 percent of the estimated mean. The chance that the true mean cost is no more than 10 percent greater or less than the estimated cost of each phase ranges from 17 to 46 percent over the different clinical phases. To have a higher chance of estimating the mean costs with no more than a 10-percent error in either direction, the sample size must be bigger.

Because the cost of one phase may be correlated with the cost of another, the precision of the estimate of total cash costs cannot be computed with the existing data (106). Thus, the precision of the total cost estimate is unknown.

ACCURACY OF SURVEY RESPONSES

The project-level studies depend on data supplied by responding companies that are unavailable from other sources. The accuracy of such data depends on two factors: the ability of firms to provide accurate data (i.e., does the company have access to accurate information?), and the motivation of firms to provide accurate data.

Clinical Period Cash Outlays--OTA’s interviews with pharmaceutical company managers indicated that, once projects reach the clinical stage, virtually all companies have project-level cost accounting systems that keep track of funds spent on speckle projects, generally identified by the chemical or biological compound. Therefore, most firms have the ability to report data on overall clinical period outlays.

OTA was unable to obtain much information about the structure of such accounting systems; hence, the ability of firms to identify expenditures by clinical phase is unclear. All companies would have an accurate picture of monthly charges to individual project accounts, however, and the dates at which phase I, phase II, and phase III trials began are available to companies, so allocation of costs by date is a reasonable approach to estimating the distribution of costs by phase. If companies responded to survey questions with this approach, the phase-specific estimates would be reasonably accurate.

Companies responding to either survey may have handled indirect, overhead, and capital costs in inconsistent or biased ways.[18] For example, in some companies the costs of a central computer may be billed to specific projects based on actual use; in others, these costs are charged to projects based on a predetermined allocation formula.

[17] A 95-percent confidence interval means there is a 5 percent chance the true mean will lie outside the interval.

Such differences in cost allocation conventions may explain part of the high variation in reported phase-specific costs among NCEs.

The money spent to acquire capital equipment and facilities used in research (referred to as capital expenditures) sometimes is not allocated to project-level management cost accounts. How companies allocated these expenses to specific NCEs for the purpose of the survey is unknown. If a responding company estimated only direct expenditures in its clinical period R&D, but included R&D capital expenditures in its total R&D expenditures, the costs in the clinical period would be underestimated, but the ratio of preclinical period costs to total R&D costs would be overestimated. Because clinical period costs occur later, the total capitalized cost would appear higher using this method. On the other hand, plant and equipment costs are always accounted for with depreciation formulas, which spread costs out for a number of years subsequent to the actual capital expenditure.[19] Because a proper cost estimate should be based on actual cash outlays, the delay in accounting for capital costs will skew expenditures toward the end of the period and will cause the total costs of R&D capitalized to the point of market introduction to be underestimated.

One hypothetical scenario that a pharmaceutical firm presented to OTA estimated that total costs capitalized to the point of market introduction could be underestimated by as much as 12 percent because of depreciation methods, but the size of the underestimate depends critically on assumptions about the initial cost of facilities and equipment, their useful life, the length of time such assets are used for the project, their remaining value at the end of the project, and the extent of shared use among different research projects.

Photo credit: THE UPJOHN COMPANY

The cost of testing NCEs in humans has risen rapidly in recent years. New diagnostic tests make for more expensive and larger clinical trials.

Preclinical Cash Outlay--Both of the project-level studies estimated the preclinical cash outlays for each sampled NCE from company survey responses to similar (but not identical) questions about annual expenditures for total NCE-oriented R&D and preclinical NCE-oriented R&D.[20] In DiMasi's study the reported ratio of preclinical to total expenditures was 66 percent, but DiMasi adjusted this estimate to 58 percent to account for trends in total spending over time. In Hansen's study the reported ratio of basic to total NCE

[18] Although the survey questionnaires did contain questions about the methods of estimating overhead, indirect, and capital costs associated with research projects, the questions were structured broadly and the study authors have provided no details about how such costing methods may have varred (109, 175).

[19] If a piece of equipment, bought new, has a 10-year life, for example, the company might charge this expenditure off at 10 Percent o' 'ts initial cost each year over the next IO years. This annual depreciation charge would then be allocated across the projects that shared in use of the capital equipment.

[20] DiMasi asked companies to report total expenditures for self-originated NCE R&D and preclinical expenditures for self-originated NCE R&D m the period 1970-86. Hansen asked companies to provide estimates of total and ' 'basic" NCE-oriented R&D conducted in the United States m the years 1962-75.

research was 51 percent. When basic research is combined with short-term preclinical animal research (estimated separately in Hansen's study) to obtain an estimate of the percent of preclinical expenditures (i.e., comparable to DiMasi), the resulting ratio is 54 percent.

The accuracy of these estimates depends both on the capability of firms to separate preclinical expenditures for NCEs from those of other products (such as combination drugs, new formulations, new drug delivery systems, etc.) and on their motivation to report such expenditures accurately.

The capability of firms to identify such preclinical expenditures would depend on the structure of their cost accounting systems. Although OTA did not have access to information on the structure of these systems in any firm, virtually all companies of reasonable size have in place project-level cost accounting systems. Projects to extend product lines of existing NCEs are probably separately identified. Any project to develop a licensed-in drug is also likely to have its own account. Separating projects among the categories required to estimate the preclinical ratio would require categorizing these projects, which can be done with a reasonable level of effort by knowledgeable personnel. Thus, it is reasonable to assume companies can slot R&D expenditures into the detailed categories needed for the estimate.

Motivation is another matter. Because the estimated ratio of preclinical cost to total R&D cost cannot be verified without an independent audit of cost accounting information, a company that understood the use to which the data would be put and with a strategic incentive to overestimate the preclinical ratio could do so without potential for discovery.

Although the firms responding to the early study may not have been aware of the potential policy uses of the study's conclusions, those responding to the later study would surely have been aware of the use to which the data would be put and its potential use in political debates. A brief review of the methods and findings of the early study could alert respondents to the importance of preclinical costs to the final full cost estimate. Thus, the motivation to overestimate this percentage cannot be discounted, especially in DiMasi's later study.

If companies responding to the DiMasi survey overestimated the percent of self-originated U.S. R&D expenditures devoted to preclinical research by 5 percentage points, so that the true percent was 53, as in Hansen's study, the estimated total cost of developing anew NCE would be $228 million in 1990 dollars, 12 percent less than the $259 million estimated by DiMasi et al.

Phase-Specific Development Times—The studies used identical methods to estimate a typical development time profile for NCEs in their sample. Responding companies reported the start date and ending date for each NCE entering a phase. The study researchers then calculated the mean phase length for all NCEs entering the phase.[21] Not only do companies have **accurate archival** records to provide these dates, but companies also must report on the start and progress of clinical testing to the FDA. Although data reported to the FDA are not in the public domain unless an NCE is ultimately approved for marketing, it is unlikely companies would deliberately misreport such data in survey responses.

The length of the period from submission of a new drug application to FDA approval was not estimated from the company survey; rather, the authors estimated average new drug application review times from the CSDD NCE database. In the early study, Hansen used the reported mean time from NDA submission to approval of all approved NCEs in the database, 24 months. DiMasi used the reported mean NDA review time for approved self-originated NCEs first tested in humans between 1970 and 1982, 30.2 months.

OTA re-estimated the NDA review period for all self-originated U.S. NCEs in the CSDD

[21] The mean phase lengths were weighted to take account of sampling probabilities.

database approved between 1967 and 1979, the time corresponding to Hansen's sample of NCEs (107).[22] The estimated approval time was 26 months. Thus, Hansen may have slightly underestimated the review time in the early study. The effect on total costs is negligible, however. Hansen's estimate would increase from $108 million to $110 million.

Companies also did not report the length of the preclinical period, but the studies' authors estimated it through other means. DiMasi used the CSDD database on approved NCEs which contains company reports on the date of first synthesis of a compound and the date of first human clinical testing. Because NCEs can be identified as self-originated or licensed-in, DiMasi was able to estimate the preclinical period for the large sample in the CSDD database of approved self-originated NCEs that U.S. firms developed during the study period. The mean estimated length of the preclinical period was 42.7 months .23

Hansen had no information at hand with which to estimate the length of the preclinical period. He simply assumed that the period was 36 months in length. OTA analyzed published CSDD data on NCEs approved between 1969 and 1982 and found the mean reported preclinical period was about 30 months. (107). A shorter preclinical period would reduce Hansen's estimated costs slightly (see table 3-5).

The preclinical period as defined by DiMasi (107) begins at the point of synthesis of a compound. Since firms must screen multiple products to obtain a lead compound (399) and engage in basic research to understand disease pathways before synthesizing a new product, this period could understate the length of the true preclinical period. If the true mean preclinical period was 5 years, the cost estimates would increase modestly (see table 3-5).

The combined impact on total capitalized costs of potential changes in the NDA review times in the Hansen study and a longer preclinical period is shown in table 3-5. The estimated capitalized costs increase modestly—by about 4 to 6 percent in both studies-as a result of these potential errors in timing.

Table 3-5--Effects of R&D Time Profile on Costs of R&D in Project-Level Studies[a] ($ 1990 millions)

Study	Capitalized cost	Percent increase (decrease) from baseline
Hansen (1979)[b]		
● Baseline estimate	$108	—
● NDA review time		
26 months	109	0).9%
● Preclinical time		
30 months	106	(1.8)
43 months	109	0.9
60 months	114	5.5
. NDA review time/preclinical time		
26 months/30 months	108	0
26 months/43 months	110	1.8
26 months/60 months	115	6.4
DiMasi et *al. (1991)*[c]		
● Baseline estimate	259	—
● Preclinical time		
60 months	270	4.2

a Estimates were adjusted for inflation using the GNP implicit price deflator.
b Cost of capital is 8 percent.
c Cost of capital is 9 percent.

KEY: NDA = new drug application.

SOURCE: Office of Technology Assessment, 1993, based on data provided in J.A.DiMasi,R.W. Hansen, H.G.Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics* 10:107-142, *1991;* R. Hansen, "The Pharmaceutical Development Process: Estimates of Development Costs and Times and the Effect of Proposed Regulatory Changes," *Issues in Pharmaceutical Economics,* R.A.Chien (cd.) (Lexington, MA: D.C. Heath and Co., 1979).

22 Hansen estimated a mean 4.5-year lag between IND and NDA submission and a 2-year period from NDA submission to approval. Therefore, the Hansen study period for NCEs first entering human trials in 1963-75 would correspond roughly to NCEs reaching approval between 1969 and 1982.

23 Although the preclinical period fo, drugs that were ultimately not approved may have been different from the period for drugs that were, OTA is unaware of any potential systematic differences that would suggest a bias in the estimate.

Success Rates—The estimated probability of reaching each clinical phase was based on survey responses. These data are both available and likely to have been reported accurately by survey respondents. Both studies predicted final approval rates not from the study sample, but from a large sample of NCEs in the CSDD database. DiMasi estimated the ultimate approval rate—23 percent—for the population of survey firm NCEs in the CSDD database that met the survey inclusion criteria. Hansen's estimated approval rate—12.5 percent—was based on all NCEs in the CSDD database covering the years of his study .24

Recently published data from the CSDD database suggest that Hansen's predicted success rate for his cohort of NCEs may have been slightly low. After 17 years of experience, approximately 14 percent of self-originated U.S. NCEs first investigated in humans between 1964 and 1975 had been approved, and further approvals were obtained later (107). A 14 percent success rate (rather than a 12.5 percent rate) would reduce Hansen's estimated capitalized cost per successful NCE by 11 percent, from $108 million to $96.2 million in 1990 dollars.

It is too early to tell whether DiMasi's predicted overall success rate will be borne out by history. The effect of the 1.5 percentage point difference in success rate on the estimated cost of Hansen's NCE sample reflects the importance of small errors either way in success rates on the ultimate cost of R&D.

Corroborating Evidence

The estimates of R&D cash outlays and capitalized costs in the project-level studies are imprecise and potentially biased, but the magnitude and net direction of these errors cannot be predicted. Therefore, OTA looked for estimates of R&D costs from independent data sources to provide additional confidence about the accuracy of the estimates from the project-level studies.

Occasionally anecdotal data come to light on the cash outlays required for the development of specific NCEs. For example, in depositions filed for a patent infringement lawsuit, Genentech claimed it had spent $45 million to develop Protropin™, its human growth hormone product, (494) and Eli Lilly certified that it had spent $16 million between 1980 and 1987 on its effort to develop its version of the drug (495). In another example, a 1980 report of the development cost of an oral systemic drug for chronic use estimated $21 million in outlays in the clinical period (226). Unfortunately, anecdotal estimates of this kind do not help verify industrywide costs, because they are self-selected and do not reflect the cost of failures or basic research.

OTA attempted to corroborate the estimates of R&D costs with two approaches. First, the industry-level studies reviewed in the previous section produced independent estimates of R&D cash outlays per success. The consistency of these studies' findings on cash outlays with those of the project-level studies is examined below. Second, data on trends in important components of R&D costs are examined to determine whether they are consistent with the rapid rise in real cash outlays implied by the two project-level studies of R&D costs.

INDUSTRY-LEVEL STUDIES

The industry-level studies help to verify the reasonableness of total cash outlays required to produce an NCE. These studies begin with aggregate R&D spending reported to PMA by its member companies (320). Because Wiggins' estimate of cash outlays per successful NCE is completely independent of data obtained in the project-level study, Wiggins is a good corroborative source.[25]

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24 Both studies used Kaplan-Meier survival curve analysis (2 19,225) to estimate the ultimate success rate in the NCE cohort under study.

25 Grabowski and Vernon's estimate of R&D cash costs is less useful for corroborative purposes than Wiggins' estimate because the estimated cash outlays are built from an assumed relationship between NCE approvals in 1 year and R&D expenditures in previous years.

Wiggins estimated cash outlays per successful NCE at $75 million (in 1990 dollars) compared with Hansen's estimate of $65.5 million (in 1990 dollars). Because Wiggins was estimating the cost of developing all NCEs, not just self-originated NCEs, his cost estimate should be conservative. The population of NCEs entering testing was somewhat more recent than Hansen's, however, and Hansen's cost estimates are based more heavily on drugs entering human testing in the earlier years of his sample. Overall, then, Wiggins' study suggests Hansen's estimated cash outlays are not out of line with the true costs and may even be slightly underestimated.

However, before one can conclude that Hansen's estimate of cash outlays is too low, it is necessary to assess the validity of the aggregate R&D data reported to and compiled by PMA and used by Wiggins in his analysis, Are these company-generated estimates accurate? PMA does not audit its member companies' reported R&D expenditures, but comparison of PMA data with publicly available financial statements suggests that R&D spending reported to PMA has increased at rates very similar to those recorded in companies' financial statements. (See chapter 2.) Although OTA cannot rule out the possibility that PMA-member firms systematically overestimate human pharmaceutical research by the same percent each year, this congruence in rates of change with audited financial records suggests the PMA aggregate R&D data are reasonably sound estimates of total R&D spending.

The total R&D spending reported to PMA includes spending not only on new drug products but also on modifications and extensions of existing products. PMA publishes the firms' reported percent of R&D devoted to new products in most years. Between 1973 and 1987 this reported percentage varied in the range of 79 to 82. Wiggins used 80 percent as an estimate of the proportion of total PMA spending devoted to NCE R&D. The accuracy of the reported expenditures cannot be verified. How companies define ''new products' is unclear; if they include follow-on products such as new formulations, the estimate could be inflated for the purpose of estimating NCE expenditures. If it is too high, then the cash outlays estimated by Wiggins would be slightly high.[26]

Although there are no industry-level studies available to corroborate DiMasi's project-level analysis, DiMasi conducted his own check on his estimates using aggregate PMA data. He allocated a portion of U.S. fins' aggregate NCE R&D costs in each year of the period 1967 to 1987 to the production of NCEs in subsequent years. Using this approach he estimated the cash outlays per successful new drug at $155 million (in 1990 dollars) compared with the survey-based method of $127.2 million. This allocation technique assumed that the production of self-originated successful NCEs would continue into future years at an average rate of 7.9 per year, despite the fact that real R&D spending rose rapidly over the period. The validity of this assumption is tenuous.

OTA did a quasi-independent check of the results of the DiMasi study using data on aggregate R&D spending by the U.S. pharmaceutical industry and the total number of self-originated NCEs introduced by pharmaceutical companies. OTA used DiMasi's estimates (109) of aggregate R&D spending on self-originated NCEs by the U.S.-based industry between 1967 and 1987, which were obtained from PMA. The total cash R&D outlays estimated in the DiMasi study ($127 million in 1990 dollars) were attributed to each self-originated NCE approved between 1979 and 1989, spread out over the time profile estimated in DiMasi's study. Total self-originated R&D expenditures for the U.S. pharmaceutical industry in 1977[27] calculated in this way were just

[26] Followup R&D conducted on existing products that have already been approved for marketing represents a real R&D cost that is not included in any of the empirical studies but which affect the company's net returns. This issue will be discussed in the next chapter on measuring returns.

[27] The year 1977 was the only one in which all self-originated NCE research would be for NCEs approved in the 1979-89 period.

5 percent less than PMA's aggregate spending estimates for that year. This result would suggest the costs, time profiles, and ratios of self-originated to total R&D found in the DiMasi project-level study are at least internally consistent with one another.

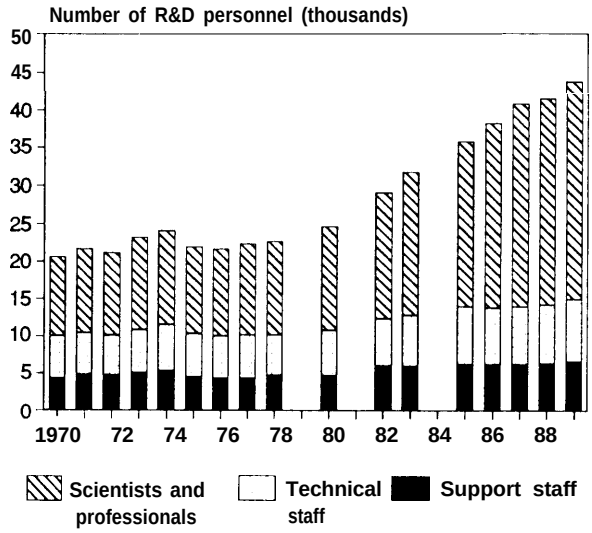
UNDERLYING COMPONENTS OF OUT-OF-POCKET COSTS

The Hansen/DiMasi studies imply that real cash outlays per successful NCE almost doubled in the 7-year period separating the midpoints of their study years, from $65.5 million to $127.2 million (in 1990 dollars). **The** increase would have been even **greater** had the ultimate success rate not improved markedly. The two surveys cover NCEs first entering human testing in 1963-75 and 1970-82. Is there any evidence to support such a rapid increase in the real costs of conducting research between the two periods? OTA examined data on three inputs to pharmaceutical R&D--research personnel, animal research subjects, and human research subjects—to learn more about the factors driving the increase in costs per successful NCE.

Research Personnel-The number of R&D personnel that PMA member firms employ remained fairly stable throughout the 1970s but began to grow rapidly in 1980 (figure 3-l). Most of this growth was in scientific and professional personnel, which numbered about 12,000 in 1977, but increased to almost 29,000 by 1989. Greater detail is unavailable **011 the** kinds of jobs these new employees performed.

As the R&D workforce grew, so grew the salaries of biomedical research personnel employed by industry (figure 3-2); however, after adjusting for general inflation,[28] salaries actually decreased a bit. From 1973 to 1979, the median annual salary of biological scientists employed by business and industry decreased from $59,961 to $52,545 (in 1990 dollars), and from 1981 to 1989 it rebounded from a low of $49,176 to $56,600.

Figure 3-1—Research and Development Personnel in Pharmaceutical Companies, 1970-89



SOURCE: Office of Technology Assessment, 1993, based on Pharmaceutical Manufacturers Association Annual Survey Reports.

If labor costs boosted the cost of bringing new drugs to market, it was largely due to the increased labor input per NCE, not wages.[29] How much of the increase in employment in the 1980s reflects increased labor inputs per successful NCE, versus adjustments for a larger field of NCEs entering each phase of clinical testing, or a greater commitment to basic research, is unknown. The most that can be said is that the trends in research personnel are not inconsistent with a substantial increase in R&D cash outlays per NCE for those NCEs frost entering clinical research in the late 1970s and early 1980s.

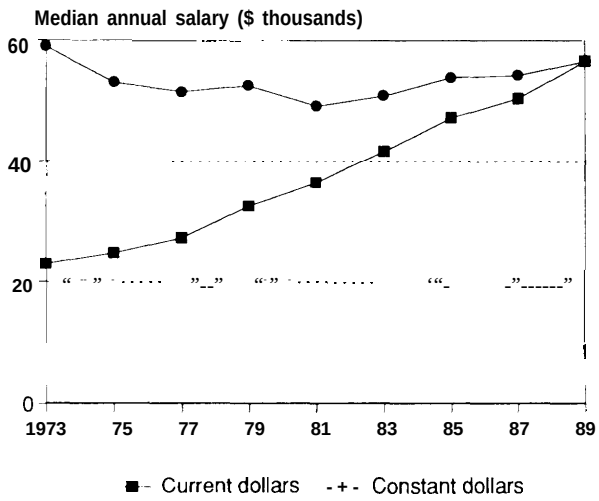
Animal Research—Although data indicate the number of some types of animals used in pharmaceutical R&D may have decreased over the last decade, other evidence is consistent with increases in the per unit costs of animal testing.

One drug company, Hoffman-La Roche, reported that the number of animals it used fell from 1 million in 1979 to just under 250,000 in 1988 (204). Data collected by the U.S. Department of Agriculture (USDA) also shows a significant

28 Inflation adjustments were made using the GNP implicit price deflator.

29 The salary data do not reflect the costs of employee benefits, however, which may have increased in real terms over the period.

Figure 3-2—Median Annual Salary of Doctoral Biological Scientists[a]



a Employed in business and industry.

SOURCE: National Science Foundation, Surveys of Science Resource Series, *Research and Development in Industry: 1987,* Detailed Statistical Tables, NSF 89-323 (Washington, DC: U.S. Government Printing Office, 1989). National Science Foundation, Surveys of Science Resource Series, *Research and Development in Industry, 1988,* Detailed Statistical Tables, NSF 90-319 (Washington, DC: U.S. Government Printing Office, 1990).

decline in absolute and relative use of animals for experimentation between 1975 and 1988 in States with a disproportionate number of industrial pharmaceutical R&D laboratories (459,460). However, these data are not definitive, since many pharmaceutical firms contract with other facilities to conduct their animal tests in other States. In addition, the USDA numbers do not include rodents, which make up the bulk of all animals employed in drug R&D, especially in the early efficacy and safety testing of potential drug candidates that companies ultimately abandon (133).

Beyond these few facts, several forces have been at work over the last 10 years to both increase and decrease the use of animals in pharmaceutical research. Because early testing involves the greatest number of animals, it also has the greatest potential for reduction. Hoffman-La Roche said most of its reduction in the use of animals came from these early phases of the R&D process. Also, improvements in *in-vitro* testing and other innovations like computer modeling (described in chapter 5) may decrease some of the demand for rodents (133),

On the other hand, an earlier OTA report concluded that alternatives to many types of animal testing are limited (447). Also, pharmaceutical executives interviewed by OTA suggested any efficiencies brought about by such innovations in the R&D process are counterbalanced by the increased number of compounds to be tested for pharmaceutical activity. In addition, the number of animals used in later safety testing is largely governed by regulatory standards.[30]

Any possible decline in the number of animals used in drug R&D in the past decade was met by significant increases in the cost of acquiring animals and conducting tests in animals. An OTA contractor surveyed 3 major commercial breeders of animals used in drug R&D and 11 laboratories that perform such research for pharmaceutical fins. Table 3-6 shows trends in the costs of

Table 3-6—Trends in the Cost of Acquiring Research Animals ($ 1990)

Species	Cost per animal 1977	1980	1987	1990	Fold increase
Rats	—	5.29	—	8.45	1,6
Mice	—	0.92	—	1.35	1.5
Guinea pigs	—	—	—	25.30	—
Rabbits	8	—	33.6	—	4.2
Dogs	195	—	—	300-500	1.5-2.6
Monkeys	391	—	—	1,000	2.6

NOTE: All crests were adjusted using the GNP implicit price deflator. Facilities surveyed were Charles River, Taconic Farms, and Hazleton. These facilities focus on breeding only. Although Hazelton conducts testing, it is carried out in a separate division.

SOURCE: Office of Technology Assessment, 1993, based on W.G. Flammand M. Farrow, "Recent Trends in the Use and Cost of Animals in the Pharmaceutical Industry," contract report prepared for the Office of Technology Assessment, April 1991.

30 See table 6-1 in chapter 6 for estimates of the number of animals typically used in each category of pharmaceutical safety testing.

Table 3-7—Price of Animal Studies[a] ($ 1990 thousands)[b]

Study	Estimated price in 1980	Price range In 1990	Fold increase	Number of Labs providing information
Acute rats	$0.8	$4-5	5-6.25	8
28-day toxicity in rats	15	30-65	2 -4.3	6
Subchronic rats	38	55-143	1.4 -3.8	8
2-year rat bioassay	384	250-575	.7- 1.5	5
Teratology rats	23	52-70	2.3 -3.0	5
Acute monkey	14	39-62	2.8 -4.4	6
Subchronic monkey	74	108-184	1.5 -2.5	6
Acute dog	2.3	22-51	9.6 -22.1	7
Subchronic dog	46	72-147	1.6 -3.2	7

a Each laboratory surveyed was given an identical protocol on which the price is based. The "cost" includes profit as well as all direct and indirect costs. Laboratories surveyed were Hazleton, Bioresearch, IIT, TSI Mason, Bio/dynamics, Pharmakon, PRI, and IRDC.
b All prices were adjusted to 1990 dollars using GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, based on W.G. Flamm and M. Farrow, "Recent Trends in the Use and Cost of Animals in the Pharmaceutical Industry," contract report prepared for the Office of Technology Assessment, DC, April 1991.

commonly used species.[31] The data indicate a significant upward trend in the real cost of acquiring all species of animals examined, with especially large increases in the costs of non-rodents.

OTA's contractor also surveyed eight facilities that conduct toxicological animals studies about the increases in their fees for tests involving various species. The results (shown in table 3-7) suggest the total costs of testing, which implicitly includes the cost of the animals' breeding, has also risen significantly over the last 10 years.

Another indicator of the potential increase in animal costs is PMA member fins' spending for safety and toxicological tests, R&D functions that use animals heavily. Between 1980 and 1989, spending for these functions went from $102 million to $565 million in 1989 dollars. Spending for safety testing increased from 7 to 10 percent of all R&D spending on human pharmaceuticals over the same 1980-89 period (321,324). However, these measures are imperfect, since not all animal testing is for safety and toxicology and not all safety and toxicology testing involves animals. The increase could reflect the increase in the number of NMEs tested for safety and toxicological effects during the 1980s.

Among the suggested reasons for animal cost increases in the OTA survey of animal research facilities are: 1) increased demands that animals be healthy and virus-free, largely eliminating the use of pound animals and explaining the particularly large increase in costs of some studies involving dogs; 2) stricter regulation of animals' living conditions under the Animal Welfare Act (most recently amended by Public Law 99-198), other government guidelines, and professional standards set by the American Association for Accreditation of Laboratory Animal Care; and 3) increased security for facilities housing animal research (133).

Research on Human Subjects—Pharmaceutical executives claim that the size of 'human clinical trials has increased dramatically over time. A rapid increase in trial sizes is consistent with an increase in the estimated cost of phase III clinical trials from $5.7 million (in 1990 dollars) for each new chemical entity (NCE) entering the phase in Hansen's study to $14.3 million (in 1990 dollars) in DiMasi's study. Part of the explanation

[31] Because each surveyed laboratory specializes in particular species, cost data for each type of animal are drawn from only one laboratory (except for dogs, which are represented by data from two breeders).

for such a large increase may be a change in the mix of drugs being tested from those for acute illness to those for chronic illness. Drugs for chronic use often require larger trial sizes.

Even within specific categories of drugs, however, the size of trials appears to have increased. OTA surveyed pharmaceutical companies for the size of clinical trials conducted prior to FDA approval for NCEs in three classes: antihypertensives, antimicrobials, and nonsteroidal antiinflammatory drugs (NSAIDs). (See chapter 6 for a more detailed discussion of the survey and its findings.) Drugs in each class approved for marketing between 1978 and 1983 were compared with those approved between 1986 and 1990.[32] Table 3-8 shows the total number of subjects entered in trials up to the point of NDA submission. The average number of subjects increased between the two periods, with the largest increase occurring in research conducted outside the United States.

Although the drugs examined in the clinical trial survey do not correspond very well to the Hansen/DiMasi research periods (only the later years of the Hansen study correspond to the approved drugs in the 1978-83 period), they do show convincingly that the number of subjects in clinical trials increased in the period between the later years of the Hansen study and the later years of the DiMasi study.

Table 3-8-Mean Enrollment in Clinical Trials Prior to New Drug Application, 1978-83 and 1986-90 (number of drugs in parentheses)

	1978-83	1986-90	Ratio of period 2 to period 1
Antihypertension drugs, . .	1,791 (9)	2,485 (9)	1,39
U.S. studies.	1,126 (8)	1,355 (9)	1.19
Foreign studies.	665 (8)	1,150 (9)	1.73
Antimicrobial.	..1,885 (15)	3,461 (12)	1.84
U.S. studies.	.1,248 (15)	2,049 (11)	1.64
Foreign studies.	637 (15)	1,412 (11)	2.22
Nonsteroidal antiflammatory drugs.	3,036 (4)	3,575 (4)	1,18
U.S. studies.	1,698 (4)	2,745 (4)	1.62
Foreign studies.	1,338 (4)	830 (4)	0.62

SOURCE: Office of Technology Assessment, 1993.

The rapid increase in the number of foreign subjects suggests that the rising cost of preapproval research may be explained in part by the globalization of research strategies over time. If U.S. firms began to prepare self-originated NCEs for entry into foreign markets earlier, and if foreign governments increased their requirements for premarket approval over time, as they did during the 1970s, the estimated cost of developing NCEs in the IND-NDA period would increase even though part of the cost increase was for approval in other markets.

Conclusions About Validity of Existing Estimates

Although the cost estimates of bringing an NCE to market are imprecise and potentially biased, corroborative evidence from the aggregate studies suggests they are not grossly overestimated. The Hansen/DiMasi studies suggest: 1) the cost of developing NCEs rose rapidly in the 1970s and 1980s, and 2) increases in the numbers of employed research personnel, the size of clinical trials and the cost of animals are potentially important causes of this rise.

Some of the observed cost increase maybe due to the restructuring of R&D into an integrated global process in the 1970s and early 1980s. U.S.-based firms became more aggressive in conducting the development required for approval of NCEs in other countries, thus compressing R&D expenditures into the pre-NDA approval phase. Nevertheless, these R&D costs, which may have been undercounted in the earlier studies because they occurred after the FDA approval date, are justifiable R&D outlays. Although the actual cash outlays required to bring a new drug to all of its potential markets may not have increased as rapidly as the studies suggest,

[32] Hansen's study years @c+ first entering testing between 1963 and 1975) corresponds roughly with introductions between 1970 and 1981. DiMasi and colleagues' study years (1970-82) corresponds roughly with introductions between 1978 and 1990.

the recent estimates of DiMasi and colleagues of the pre-FDA approval cash outlays are reasonably accurate.

Can more or different kinds of studies improve on the existing estimates? More careful analysis of project cost accounts and adjustment of estimates for different cost allocation rules would give a more consistent estimate across firms, but it is unlikely the resulting estimates of cash outlays would be very different, and probably not lower.

Gaining access to proprietary company management cost accounts in a large enough number of companies would be very costly and would take many years. Although Congress has the power to subpoena financial data, pharmaceutical companies have demonstrated a willingness to actively resist providing access to this proprietary data. Past efforts of the U.S. General Accounting Office to obtain data on pharmaceutical costs were ultimately unsuccessful after many years of effort that ultimately involved decisions in the U.S. Supreme Court. (See appendix D for a history of the court cases and a legal analysis of congressional access to pharmaceutical companies' financial data.)

To summarize, the estimates by DiMasi and colleagues of the cash outlays required to bring a new drug to market and the time profile of those costs provide a reasonably accurate picture of the mean R&D cash outlays for NCEs first tested in humans between 1970 and 1982. The rapid increase in inflation-adjusted R&D cash outlays over the relatively short observed time span separating Hansen's and DiMasi's studies illustrates how quickly such costs can change and how sensitive such costs are to changes in R&D success rates over time.

OTHER FACTORS AFFECTING VALIDITY

The Cost of Capital

Capitalizing costs to their present value in the year of market approval more than doubles the cost of R&D as estimated by DiMasi and colleagues, from $127 million (in 1990 dollars) for cash R&D outlays per successful drug to $259 million (at a 9 percent interest rate). While the practice of capitalizing costs to their present value in the year of market approval is a valid approach to measuring R&D costs, little is known about the appropriate cost of capital for R&D projects.

A completely accurate measurement of capitalized cost would require the analyst to know, for each dollar spent on the particular sample of NCEs studied by DiMasi, the cost of capital that pertained to that investment at the time it was made. Even though these are retrospective studies, the cost of capital that should be assigned is the cost the investors actually faced at the time they made their investments.

The cost of capital varies widely across types of research projects and with successive investments as the project progresses toward the market. (See appendix C for an explanation.) It also changes from day to day as the risk-free interest rate changes. But detailed data on the actual riskiness of particular projects invested at specific times simply do not exist. Consequently, the fully capitalized cost of R&D associated with the NCEs entering testing in DiMasi's study can be only crudely approximated.

All of the R&D cost studies reviewed in this chapter assumed the cost of capital for R&D investments was constant across all projects and over the entire period during which the R&D spending on the sampled NCEs was taking place. Myers and Shyam-Sunder estimated for OTA the inflation-adjusted weighted average cost of capital for a sample of pharmaceutical firms at three points in time, January 1, 1980, January 1, 1985, and January 1, 1990, at 9.9, 10.7 and 10.2 percent respectively (285). For pharmaceutical companies as a whole, then, a reasonably rough approximation for the cost of capital over the period of DiMasi's study would be 9 to 10 percent. (The higher the cost of capital, the higher would be the estimated R&D cost, so DiMasi's choice of 9 percent is conservative in that regard.)

Pharmaceutical firms can be thought of as collections of investments, some with high risk and some with low risk. R&D investments are

riskier than other investments pharmaceutical companies make, but for reasons that are different from conventional ideas about risk (see appendix C for explanation). The earlier in the R&D process the investment is (e.g., at the preclinical phase of research), the higher its cost of capital is likely to be. How much riskier R&D investments are than the other investments of the firm cannot be precisely estimated with existing data, however. The best that can be done to get a quantitative estimate of the cost of capital for pharmaceutical R&D projects is to examine the cost of capital for firms investing largely in R&D and having relatively little investment in ongoing operations.

Myers and Shyam-Sunder estimated the real cost of capital for seven small pharmaceutical fins, three of which were biotechnology fins, at 14 percent, 4 percentage points higher than the cost of capital for 15 large pharmaceutical companies. In an unrelated study, Stewart (409) estimated the cost of capital for business risk for 1,000 publicly traded companies in the United States and Canada. Companies whose main business was providing R&D services (R&D laboratories) had a cost of capital for business risk approximately 4.5 percentage points higher than the cost of capital for business risk for the drug companies in Myers and Shyam-Sunder's sample. Shyam-Sunder's recent update of the Myers and Shyam-Sunder paper found a 2.6 percent difference in the net cost of capital between 30 biotechnology firms and 19 large pharmaceutical firms (390).[33] The results of these studies suggest that a 4 percent differential in the cost of capital from the beginning to the end of the research process is a reasonable upper bound for the capitalized costs of early R&D.

The weighted average cost of capital for pharmaceutical firms with ongoing operations (after adjusting for inflation expectations) was roughly 9 to 10 percent over the past 15 years. Investments in manufacturing capacity should therefore be below that value, while R&D investments should be above it. A reasonable upper bound on the true cost of capital for early pharmaceutical R&D can be constructed by assuming investments in a manufacturing plant have a 10 percent cost of capital (a high estimate). Applying the 4 percent spread (a relatively high estimate) to the 10 percent cost of capital, the real cost of capital for early R&D would be no greater than 14 percent.

OTA recalculated DiMasi's study with a cost of capital that decreases linearly over the life of R&D projects from 14 to 10 percent. The resulting capitalized cost in DiMasi's study increases from $259 million to $359 million (in 1990 dollars). Thus, an upper bound on the full cost of bringing NCEs to market in the 1970s is roughly $359 million. These calculations highlight the sensitivity of the estimate of fully capitalized R&D costs to assumptions about the cost of capital for R&D.

TAX SAVINGS FROM R&D

A company's effective cost of bringing a new drug to market is substantially reduced by tax savings the company (or its investors) receives when it invests in R&D. The net cost of every dollar spent on research must be reduced by the amount of tax avoided by that expenditure. These tax savings from R&D come about both from deductions and from tax credits that reduce a company's tax liability when it spends money on R&D.[34]

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33 A 1989 survey of approximately 145 biotechnology firms engaged in therapeutic health markets reported R&D expenses accounted fOr 67 percent of product sales (64).

34 Companies get tax breaks from a number of provisions in the Federal tax code that effectively reduce the amount of taxes they owe On earned income. (See chapter 8 for details.) Some of these tax savings are not influenced by the amount of money the company invests in R&D. For example, companies that manufacture products in Puerto Rico and other U.S. possessions can take advantage of a tax credit on income from those operations (see chapter 8). The amount of the possessions tax credit that can be claimed is unaffected by how much R&D the company performs. Thus, the effect of taxes on the cost of R&D must be computed as if the possessions tax credit did not exist. Only those tax savings that come about from conduct of R&D should be included in the analysis.

Table 3-9--U.S. Corporate Marginal Tax Rates, 1971-91

Taxable Income ($)	1971-74	1975-78	1979-81	1982	1983	1984-86	1987[a]	1988-91
0-25,000	22	20	17	16	15	15	15.0	16
25,000 -50,000	48	22	20	19	18	18	16.5	16
50,000 -75,000	48	48	30	30	30	30	27.5	25
75,000-100,000	48	48	40	40	40	40	37.0	34
100,00-335,000	48	48	48	46	46	46	42.5	39
335,000-1,000,000	48	48	48	46	46	46	40.0	34
1,000,000-1,405,000	48	48	48	46	46	51	42.5	34
1,405,000+	48	48	48	46	46	47	40.0	34

[a] 1987 tax rates were based on average rates paid in 1986 and 1988. Figures shown are the average or rates paid by all firms in 1987.

SOURCE: U.S. House of Representatives, U.S. Congress, 'The Overview of the Federal Tax System," 102d Congress (Washington, DC: U.S. Government Printing Office, April 10, 1991).

Under section 174 of the Federal tax code, qualifying R&D expenses are deductible from taxable income. This tax deduction reduces the cost of qualifying R&D by the amount of the company marginal tax rate.[35] Table 3-9 presents the U.S. corporate marginal tax rates for the years 1971 to 1991. Because of the size and sales of most major pharmaceutical firms, the bulk of their taxable income would fall into the highest tax bracket.[36] Hence, in the simplest analysis, the cost of R&D spending should be reduced by the top tax rate.[37] Between 1971 and 1991, this marginal tax rate fell from 48 to 34 percent, thus effectively raising the cost of R&D. (It also raised the after-tax revenues from products resulting from the R&D, so the importance of taxes is not nearly as great when measuring net R&D returns, rather than R&D costs in isolation.)

In the R&D period covered by DiMasi (1970-87), the rate declined from 48 to 46 percent. With a 46-percent tax rate, the after-tax cost of $1.00 of R&D undertaken at the time of DiMasi's study would be: $1.00-$0.46 = $0.54.[38] Today, the net cost of a dollar of R&D undertaken by an established company with positive net income would be $0.66.[39]

During the 1980s two tax credits were put into effect that reduce the cost of pharmaceutical R&D. In 1981, Federal tax law was amended to include a tax credit for any firm when it increases "qualifying" R&D expenses. This credit carried a statutory credit rate of 25 percent of qualifying

35 If a firm conducts R&D in other countries that allow R&D to be deducted from taxable income but have tax rates that differ from those in the United States, the company may realize a different net rate of reduction in the cost of its R&D.

36 Since the firms studied by Hansen and DiMasi made up 40 percent of domestic R&D, they were probably composed largely of well established pharmaceutical firms.

37 Unlike other R&D expenses that are deducted in the year they are made, capital expenditures for R&D, such as new R&D equipment or facilities, are depreciated from taxable income over several years. The shorter the period of depreciation the greater will be the effect of tax savings on the cost of R&D. Prior to 1981, Federal law required firms to deduct R&D capital expenditures in equal amounts over the useful life of the equipment or building, which could be 10 years or more. Beginning in 1981, firms could fully depreciate R&D capital expenditures within 3 years, although in 1986 Congress raised the period to 5 years. Not much is known about the depreciation schedules used to estimate R&D costs in the Hansen and DiMasi studies. Depreciation schedules on tax returns maybe different from those for financial statements, and without more detailed information it is impossible to know whether the net tax savings for R&D capital expenditures are higher or lower than the statutory marginal rate. OTA assumed for the analyses here that R&D capital expenditures are taxed at the marginal tax rate.

38 As explained in chapter 8, not all R&D expenses meet the definition of 'qualifying'' laid out in section 174 of the tax code. This definition becomes important for calculating the orphan and R&D tax credits discussed below. However, it is not important here for calculating the deduction, because R&D expenses not deductible under section 174 are nonetheless deductible as other business expenses.

39 Small startup biotechnology f,, may have little or no taxable income, but tax losses can be carried forward into future years. Still some firms may never become profitable, and the value of future tax benefits is less than those that can be used immediately. Therefore, the net cost of research to such small firms may be higher than for established pharmaceutical fins.

expenses until 1986, when the rate was reduced to 20 percent. The credit pertains only to increases in R&D, not to actual expenditure levels, so the extent to which it actually reduces the cost of R&D would depend on research spending trends in firms themselves. Because pharmaceutical R&D grew rapidly in the 1980s, the pharmaceutical industry may have benefited more than other industries from the R&D tax credit.

The Orphan Drug Act of 1983 (Public Law 97-414) provided a 50-percent tax credit for qualifying clinical R&D on investigational drugs that have been granted orphan status by the FDA. The credit is available only for "qualifying" clinical research, not for animal or laboratory research and not for supervisory or other kinds of R&D expenditures typically disallowed by the Internal Revenue Service. Also, when the credit is applied, the expenses cannot be deducted, so the net cost of a dollar of qualifying research under this credit is effectively $0.50. Companies without current taxable income cannot save the credit for use in future years, however, so startup research-based firms may not have access to this credit.

Because these credits are of recent vintage and would not apply to the vast part of the research undertaken in the time periods studied by Hansen and DiMasi, they would not affect the net costs of that research. Chapter 8 contains estimates of the extent to which these credits have been claimed in recent years.

To illustrate how important tax savings are to net R&D costs, OTA recalculated the R&D cost per new chemical entity from DiMasi's estimates (table 3-10). The sample of NCEs that DiMasi studied underwent the great bulk of discovery and development at a time when the marginal tax rate was 46 to 48 percent. Adjusting for tax savings (using a 46-percent rate) without any other changes reduces the net cash outlays per NCE from $127.2 million to $65.5 million, and it reduces the total costs capitalized to the point of market introduction from $259 million to $140 million. When the cost of capital was permitted to decrease linearly from 14 to 10 percent over the life of the R&D projects, the net after-tax cost was $194 million. This estimate is an upper bound on the cost of bringing new drugs to market for products that frost entered human testing in the 1970s.

Table 3-10-After-Tax R&D Costs Estimated by DiMasi Under Different Assumptions About the Cost of Capital" ($ 1990 millions)

Cost of capital (%)	Before-tax savings	After-tax savings (46%)
9	$258,650	$139,671
10	279,112	151,045
Variable (10 - 14)	359,313	194,029

a All assumptions, given in 1990 dollars, were adjusted for inflation using GNP implicit price deflator.

SOURCE: Office of Technology Assessment, 1993, estimates adapted from J.A. DiMasi, R.W. Hansen, H.G. Grabowski, et al., "The Cost of Innovation in the Pharmaceutical Industry," *Journal of Health Economics 10:107-142, 1991.*

Lower tax rates in the 1980s would raise the net costs of research, all other things being equal, to as much as $237 million in after-tax dollars, but because R&D outlays per successful drug are extremely sensitive to changes in technical and regulatory conditions, it is impossible to predict the cost of R&D for projects beginning today. The rising number of biotechnology-based drugs under investigation in recent years (see below) may radically alter the time and expenditure profile in ways that can not be predicted from the DiMasi study.

RECENT TRENDS IN THE COST OF R&D

The studies of R&D costs reviewed in this chapter examined NCEs that entered testing in the 1960s and 1970s. There are few data sources, outside of aggregate R&D expenditures, to establish trends for drugs that entered clinical research in the 1980s. As the previous chapter described, R&D spending climbed dramatically in real terms throughout the 1980s, but the ultimate impact of these spending increases on the cost of developing NCEs will depend on the productivity of the research in bringing promising NCEs into clinical testing and ultimately to market.

OTA compared recent data (from the 1980s) on the outputs of pharmaceutical research, the length

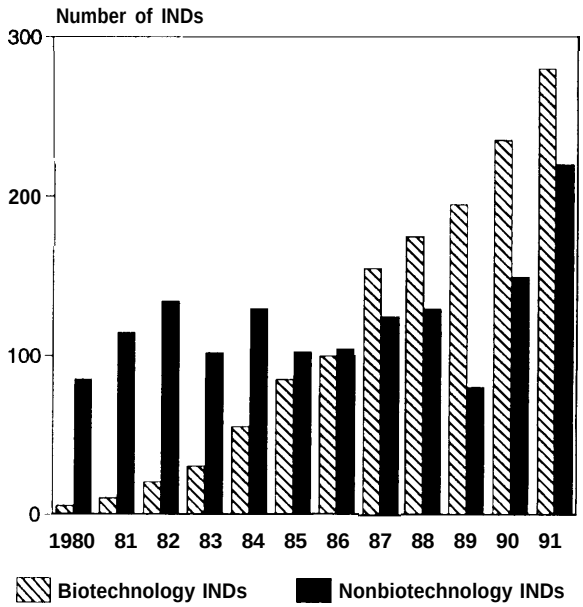
of the development period and success rates for NCEs with data from the 1970s. overall, the data suggest the output of preclinical research-the submission of investigational new drug applications for new molecular entities—has increased in the 1980s. Moreover, the rate of success in reaching the NDA stage or market approval has improved for NCEs introduced in the 1980s. However, the higher success rates for NCEs may be partly driven by an increase in the proportion of INDs for licensed-in drugs.

Trends in Commercial INDs for NCEs

Data published by the FDA Center for Drug Evaluation and Research show the total number of commercial INDs handled by the Center increased from an average of 253 per year between 1975 and 1980 to 334 per year between 1981 and 1990.[40] (See chapter 6 for more detail.) Because the same NCE, may have multiple INDs, and new uses or formulations of existing drugs also require INDs, the total number of INDs is not a perfect indicator of increases in the number of NCEs entering clinical development. Data from CSDD'S NCE survey of over 40 companies indicate the number of INDs for NCEs increased from 210 per year in 1975-78 to 299 per year in 1983-86 (107).[41] Although INDs for U.S. self-originated NCEs grew by 25 percent between the periods, the percent of all NCE INDs that was for self-originated drugs declined from 60 to 53 percent between the two periods. Licensed-in drugs and INDs submitted by foreign firms grew as a proportion of total NCE INDs submitted to the FDA.

Not only did the number of INDs increase rapidly throughout the 1980s, but the makeup of the drugs shifted from chemically synthesized compounds to biotechnology drugs (see figure 3-3) (66). This substantial shift means that the technologic and regulatory conditions that influence drug R&D costs have changed in the decade

Figure 3-3-Biologic Applications for Investigational New Drugs, Fiscal Years 1980-91



SOURCE: Federal Coordinating Council for Science, Engineering, and Technology, Office of Science and Technology Policy, Executive Office of the President, *Biotechnology for the 21st Century: A Report by the FCCSET Committee on Life Sciences and Health* (Washington, DC: U.S. Government Printing Office, February 1992).

of the 1980s. Success rates, regulatory delays, the length of the preclinical and clinical period, and costs of clinical research may be vastly different for these new drugs. Prediction of today's cost of bringing a new drug to market on the basis of the kinds of drugs that were being tested in the 1970s —the period of DiMasi's study-is bound to be inaccurate.

Trends in Success Rates

Data CSDD supplied on NCEs developed by companies responding to its ongoing survey indicate the probability of reaching the NDA stage was higher for NCEs first entering clinical testing between 1980 and 1982 than it was for NCEs first entering clinical testing in the 1970s.

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40 The published IND numbers do not include biologicals, because the Center for Biologics does not compile such data. Biological products under development were few in the 1970s, but grew rapidly in the 1980s.

41 DiMasi and colleagues also give information on the 1979-82 period. See chapter 6 for more detail.

Table 3-11 shows the proportion of NCEs in the CSDD sample for which an NDA was filed within 48 or 60 months of IND filing for four cohorts of NCEs first entering clinical testing.[42] In addition, the FDA supplied OTA with more recent data on a sample of NCEs whose frost commercial INDs were filed in the 1984-86 period that were compared with an earlier published FDA analysis of a similar group of INDs first filed 1976-78. INDs reaching the NDA filing stage within 54 months increased from 6.8 to 11 percent. (Though few NMEs were approved from the 1984-86 cohort, the overall approval rate was also higher. See chapter 6 for more detail.)

Although overall success rates have improved in the recent past, the improvement may be due in part to a shift in NCEs from self-originated to licensed-in. Licensed-in drugs have higher success rates than do self-originated drugs, probably because they are self-selected for success. For example, of NCEs entering testing between 1970 and 1982, an NDA was submitted within 48 months for 7 percent of self-originated drugs, compared with 21 percent of licensed-in drugs (427). At 60 months, 28 percent of licensed-in NCEs had reached NDA submission compared with 9 percent of self-originated drugs. Of NCEs entering human testing among U.S. companies, those licensed-in grew from about 21 percent in 1975-78 to 27 percent in 1983-86 (107). Thus, the improvement in success rates for drugs first entering testing in the 1980s is at least partly due to the changing source of NCEs.

Table 3-n-Percent of NCEs Reaching NDA/PLA Submission in Given Time Intervals

Year in which NCE entered clinical trials	Percent filing NDA/PLA within: 48 months	60 months
1965 -69.	4.6%	7.0%
1970 -74.	8.0	12.0
1975 -79.	10.0	13.0
1980 -82....., ...	12.0	17.0

KEY: NCE = new chemical entity; NDA = new drug application; PLA = product license application.

SOURCE: Office of Technology Assessment, 1993, based on data supplied by Tufts University Center for the Study of Drug Development from its database of NCEs reported by 41 pharmaceutical firms.

Recent Development of Orphan Drugs

Since 1983, Federal law has stimulated the development of orphan products through a series of incentives and subsidies, including the tax credit for clinical research on designated orphans drugs. (See chapters 8 and 9 for more detail.) These products may have a very different cost structure from other NCEs, not only because of the tax credit but also because they may involve smaller and shorter clinical trials than other drugs. Although FDA approval standards are no different for this class of drugs than for others, orphan drugs are likely to have smaller and quicker clinical research studies than other studies because of the relative rarity of the diseases studied.

The FDA provided OTA with confidential data on new molecular entities (NMEs) whose first commercial IND was filed in the years 1984-86. (See chapter 6 for more detail on this sample of drugs.) Within 54 months of the IND filing, an NDA had been filed for 11 percent of all INDs, and 3.8 percent had been approved (see chapter 6), whereas for NMEs that had orphan designations, an NDA had been filed within 54 months for 33 percent, and 11 percent had been approved.[43]

Regulatory approval times also appear to be shorter for orphan drugs. For example, during the period 1985-90, the average approval time for approved drugs without orphan designation was 29.3 months, while for approved orphan drugs it was 27.4 drugs (168). For products classified as "A" by the FDA, the approval time for non-orphans was 25.7 months, while for orphans it

[42] A regression of NDA filing rates on time indicated the increase shown in the table was statistically significant at the 10 percent level Of significance for both the 48-month and 60-month success rates.

[43] OTA identified nine NMEs for which the first commercial IND had been filed in 1984-86, and which had been granted an orphan designation. An additional four NMEs in the IND cohort had orphan designations, but data on the sponsoring company were inconsistent and they were not used. (Exclusion of the four NMEs did not change the results materially.)

was 18.1 months (168). Although it is impossible to know whether the ultimate success rate for orphan products will be higher or lower than for nonorphans, the sensitivity of development costs to success rates suggests orphan drugs may have a substantial cost advantage.

CONCLUSIONS

The increase in the inflation-adjusted cost of developing anew drug from the early 1970s to the late 1970s is dramatic. Real cash outlays per successful NCE increased by almost 100 percent in the period. The evidence suggests that, in 1990 dollars, the mean cash outlay required to bring a new drug to market (including the costs of failures along the way) was in the neighborhood of $127 million for drugs first entering human testing in the 1970s. The size of this required cash investment depends on the rate of success at each stage of development and the ultimate productivity of the research enterprise. Small differences in the ultimate success rate can make a big difference in the cost per approved NCE. Other factors, such as changes in R&D technology and regulatory conditions, can also have dramatic and rapid impacts on costs. Thus, the estimates of the R&D cost per successful product are inherently unstable over time.

The fully capitalized cost of bringing a new drug to market cannot be measured with great accuracy because the cost of capital for R&D investments is unknown. The best evidence suggests, however, that for drugs first entering human testing in 1970-82, the after-tax cost per successful drug, capitalized to the point of FDA approval for market, was somewhere between $140 million and $194 million (in 1990 dollars).